

Acute and Short-Term Effects of a New Calcium Antagonist in Hypertension

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SUMMARY Nitrendipine (Bay e 5009) is a new calcium antagonist antihypertensive agent similar in structure and function to nifedipine. Nitrendipine was tested in a range of single and repeated doses in 10 adult males with uncomplicated mild to moderate hypertension. The treatment goal was reduction of diastolic blood pressure to 90 mm Hg or less. The dose that achieved goal blood pressure ranged between 10 and 30 mg. Systolic and diastolic blood pressure began to fall within 15 minutes following ingestion of single oral doses of nitrendipine. The maximum effect of the drug was achieved in 60 to 90 minutes and remained at approximately this level for 6 to 8 hours. The average reduction in supine diastolic was more than twice as great as the fall in systolic blood pressure. With continuous doses given three times daily, all patients' blood pressures were as low or lower than the maximal effect observed after single doses. The reduction in blood pressure was sustained for the full 3 weeks of treatment. There was a sustained small increase in pulse rate averaging 6 beats/min. The drug was generally well tolerated by most patients. Mild to moderate headache that resolved with continued treatment was the most frequent side effect. This preliminary trial indicates that nitrendipine is an effective antihypertensive agent that merits further study. (Hypertension 4 (suppl II): II-32-II-35, 1982)

KEY WORDS • nitrendipine • Bay e 5009 • vasodilators •
diastolic blood pressure • side effects

NITRENDIPINE (Bay e 5009) is a new calcium channel blocking agent currently undergoing Phase I testing in the United States. It is a dihydropyridine derivative with a chemical structure and mechanism of action similar to that of nifedipine.¹ Previous studies in Germany and Argentina have indicated that it depresses the slow depolarizing current, acts as a vasodilator, and causes a slight increase in cardiac output. It has been generally well tolerated by patients; headache and flushing have been the only commonly reported side effects.

Methods

This study was designed to determine the general tolerance and activity of nitrendipine in a range of single and repeated doses. The subjects of the study were adult males with mild to moderate hypertension with no evidence of major target organ impairment. The patients admitted to the trial exhibited supine

baseline blood pressure (mean of three separate visits) ranging between a diastolic > 95 and < 115 mm Hg. The goal of therapy was to lower the supine diastolic blood pressure to 90 mm Hg or below.

All patients underwent a 3-week baseline evaluation period during which a complete history, physical examination, and baseline laboratory profile were obtained and weekly measurements of supine and standing pulse rate and blood pressure were made. If antihypertensive drugs were being taken they were withdrawn for a 2-week "washout" period preceding the baseline period of the study. Pulse rate and blood pressure were measured at intervals of no more than 1 week during the washout period. Baseline laboratory data included the standard 12-lead EKG, a complete blood count including a differential and platelet count, plasma glucose, sodium, potassium, chloride, uric acid, blood urea nitrogen, creatinine, SGOT, SGPT, alkaline phosphatase, bilirubin, LDH, CPK, and urinalysis.

The first five patients recruited into the study were brought to the laboratory in the morning where they were given a single oral dose of 5 or 10 mg of nitrendipine and observed for 8 hours. Supine and standing pulse rate and blood pressure were recorded at intervals of 15 minutes for the first hour, then at 30-minute

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intervals for the next 3 hours, and then hourly. Patients returned at weekly intervals to repeat the single dosing procedure with progressively larger doses of nitrendipine until goal blood pressure was attained, intolerable side effects developed, or a maximum dose of 30 mg was given. Side effects were elicited by interview, and EKGs were obtained at each visit before and after the drug was given. The baseline blood tests were repeated at least once during the Single Dose Phase of the study.

After the dose was found that resulted in goal blood pressure, the patients were given this dose three times daily as outpatients. Patients were seen 2 days after beginning the outpatient therapy and then 5 days after that. Pulse rate and blood pressure were measured at each visit.

The first five patients continued taking the medication for an additional 2 weeks, with visits to the clinic once per week. Five additional patients who met the same selection criteria as the first group were started on treatment with 10 mg three times daily. They were seen 2 days later and if goal blood pressure had not been attained the dose was increased by 5 or 10 mg increments at intervals of 3 to 5 days until control was achieved. They then continued taking the medication for 2 weeks, with weekly clinic visits. Each patient was seen 2 days after completing the study, for a final physical examination.

Results

The 10 participants in the study had the following baseline characteristics, given as means \pm standard deviation: age 52 ± 6 years, supine systolic blood pressure 160 ± 15 mm Hg, supine diastolic pressure 104 ± 6 mm Hg, supine pulse rate 77 ± 8 beats/min, erect systolic pressure 160 ± 11 mm Hg, erect diastolic pressure 107 ± 7 mm Hg, and erect pulse rate 82 ± 7 beats/min.

Figure 1 shows the maximum reduction in diastolic blood pressure achieved by individual patients in the supine position after single oral doses of nitrendipine. The magnitude of the antihypertensive effect increased with increasing doses within the range of dosages used in this study. The average reduction in supine diastolic pressure was 29 mm Hg or 28%. The response of the supine systolic pressure was similar but of lesser magnitude, that is, 23 mm Hg average fall or a 15% reduction. Pulse rate in the supine position increased an average of 9 beats/min above baseline after nitrendipine but did not increase progressively with increasing dosage. Similar results were obtained for the blood pressure and pulse rate recorded in the erect position. The magnitude of the changes in mean systolic blood pressure and pulse rate were greater in the erect than in the supine position. The reverse was true for the diastolic blood pressure.

The mean percentage reduction in supine diastolic blood pressure over time for the five patients who received single doses of nitrendipine is shown in figure 2. The dosage given was that at which individual

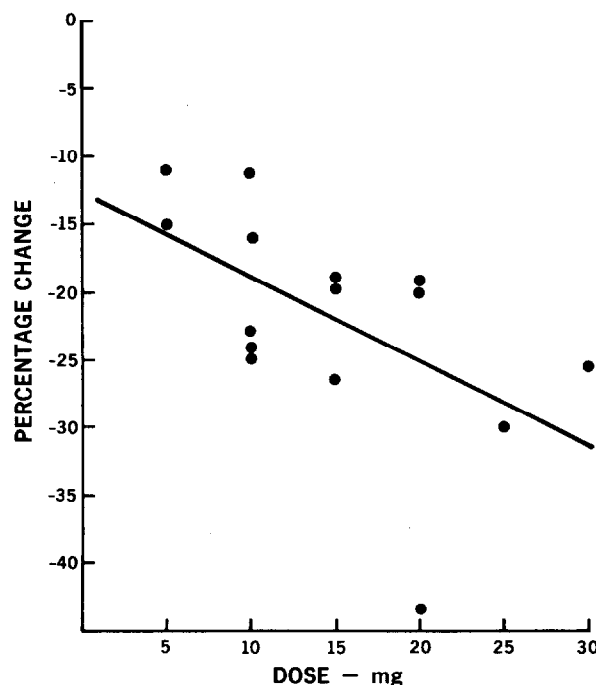


FIGURE 1. Percent reduction in supine diastolic blood pressure achieved with different doses of nitrendipine. Linear regression line shown.

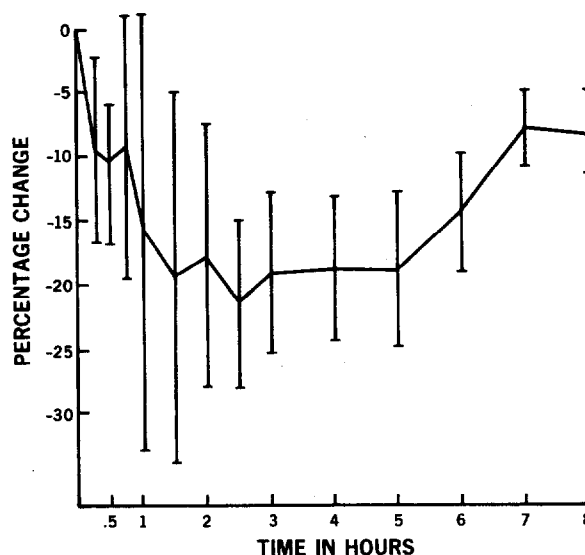


FIGURE 2. Percent reduction in supine diastolic blood pressure achieved at different times after ingestion of a single oral dose of nitrendipine (mean \pm standard deviation).

patients achieved the goal diastolic pressure of 90 mm Hg or less in the supine position. Blood pressure began to fall within 15 minutes after oral ingestion. The maximum effect of the drug was achieved in 60 to 90 minutes and persisted for 6 to 8 hours. The reduction in supine diastolic blood pressure averaged 19%, which represents a 20 mm Hg fall from the baseline mean of 105 mm Hg. The reduction of the supine systolic pressure was again similar but of lesser magnitude, averaging 7% for the group. The reductions in blood pressure in the erect position were slightly greater for the systolic and slightly less for the diastolic blood pressure as compared to the supine recordings. However, the onset and duration of effect were the same.

With continuous dosage during the outpatient phase of the study, the reduction in supine diastolic blood pressure was nearly the same as that observed following single doses. The reduction averaged 16% and was sustained for the full 3 weeks of treatment without any evidence of drug resistance (fig. 3). The reduction in supine systolic pressure averaged 14%, which was somewhat greater than that attained during the single dose phase of the study. The reduction persisted for the full 3 weeks of treatment. Similar reductions in

blood pressure were obtained in the erect position. There also was a sustained small increase (averaging 6 beats/min) in both the supine and standing pulse rates. All patients exhibited a reduction in supine diastolic pressure greater than 10 mm Hg on at least one visit during the outpatient phase of the study. Goal blood pressure was attained by 90% of the patients, that is, a supine diastolic blood pressure of 90 mm Hg or less on at least one outpatient visit, and was attained on all except one outpatient visit by 80%. The minimally effective dose, that is, the dose at which a definite reduction in blood pressure was first seen, was between 5 and 10 mg. The optimal dose, defined as the dose at which goal pressure was attained, ranged from 5 to 30 mg, with a mean of 17 mg, three times daily.

Side effects reported during the single dose laboratory phase were limited to headache in four of five patients and transient dizziness in one of five. The headache was frontal, of mild to moderate severity, and resolved spontaneously in 1 to 3 hours or sooner than that following aspirin. During the continuous dosage outpatient phase of the study, five of 10 patients reported headaches, one of whom also reported palpitations. These symptoms usually resolved as patients continued to take the medication; no patient discontinued the drug because of side effects.

One patient while on medication reported the gradual onset of fatigue on mild exertion, which was most pronounced in the legs. This symptom disappeared after the drug was discontinued at the end of the study. Subsequent investigation revealed that the patient had a pre-existing peripheral neuropathy which may have predisposed him to the development of this symptom. Another patient developed multiple symptoms including headache, fatigue, abdominal cramps, nausea, and constipation. These symptoms were accompanied by new t-wave inversions in the lateral precordial EKG leads. There were no elevations of SGOT, LDH, or CPK in association with these symptoms. All abnormalities returned to normal after the medication was discontinued. The greater severity of symptoms experienced by these two patients was not correlated with medication dose or blood pressure response. The first patient was taking only 5 mg of the drug and still exhibited an excellent antihypertensive response. On the other hand, the second patient was receiving one of the highest doses but did not achieve goal blood pressure.

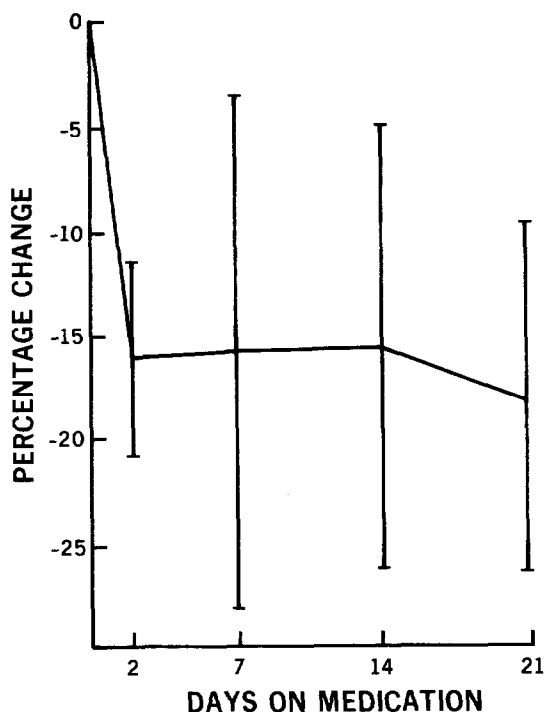


FIGURE 3. Percent reduction in supine diastolic blood pressure achieved at different times during continuous outpatient treatment with nitrendipine (mean \pm standard deviation).

Discussion

Calcium channel-blocking drugs inhibit the movement of calcium from the extracellular to the intracellular environment. This results in a reduction in myocardial contractility and in smooth muscle tone including the coronary and peripheral arteries as well as an inhibition of nerve conduction in the heart. Certain of the compounds, such as verapamil, exhibit increased blocking activity on the cardiac conduction

system. Nifedipine, on the other hand, exerts a marked effect on blocking calcium entry into vascular smooth muscle. Several investigators have found nifedipine to be highly effective in treating severe hypertension.²⁻⁵ Nitrendipine, like nifedipine, is a dihydropyridine derivative and shares many of the pharmacological properties of the latter drug. Nitrendipine lowers blood pressure in renal hypertensive and spontaneously hypertensive rats in doses of 0.1 mg/kg and higher.¹ In Goldblatt hypertensive dogs, doses of 0.03 to 1 mg/kg orally were effective. The drug produced marked vasodilation in the femoral and coronary vascular bed, less in the splanchnic bed, and none in the vasculature of the skin.¹ Nitrendipine thus acts as a vasodilator with its most marked effect in muscle.

Vasodilator drugs that have their main effect on arterioles rather than veins, such as hydralazine, characteristically exert a greater depression of diastolic than of systolic blood pressure.⁶ This is probably due to the fact that diastolic blood pressure is dependent primarily on peripheral vascular resistance, which is greatly reduced with vasodilator drugs such as nitrendipine. Systolic blood pressure, on the other hand, is more dependent on cardiac output than is the diastolic. Since cardiac output characteristically increases after arteriolar dilator drugs are given, systolic pressure will not fall as much as diastolic blood pressure.

Phase I clinical trials, such as the present study, can only provide a preliminary impression of the efficacy and safety of a new drug. Viewed in that light, the clinical responses to nitrendipine as an antihypertensive agent appear sufficiently promising to warrant further investigation.

Summary

Nitrendipine is a new antihypertensive agent similar in structure and function to nifedipine. In this study it was effective in reducing supine and standing systolic and diastolic blood pressure while inducing only a modest increase in heart rate. Its effect on blood pressure was sustained for the 3 weeks of observation. The drug was generally well tolerated by most patients. Mild to moderate headache that resolved with continued treatment was the most frequent side effect. This preliminary trial indicates that nitrendipine is an effective antihypertensive agent. Additional studies will be needed to clarify its long-term efficacy and toxicity.

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